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New Analysis Showed Early Patient Response to Forteo in Postmenopausal Women with Osteoporosis

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Changes in Bone Markers at One Month may Provide Important Information about FORTEO's Early Benefits

Changes in markers of bone remodeling after one month of treatment with FORTEO® (teriparatide [rDNA origin] injection) may provide important early evidence of treatment response, according to new data presented today at the 86th Annual Meeting of The Endocrine Society (ENDO).

The Fracture Prevention Trial, (FPT), a registration trial for FORTEO, was a randomized, double-blinded, placebo controlled study that enrolled 1,637 women with osteoporosis. Subjects were randomized to FORTEO 20 mcg/day, (the currently approved and marketed dose), FORTEO 40 mcg/day or placebo for a median of 19 months.

The sub analysis of 527 patients from the F P T (previously published in the *New England Journal of Medicine*, May 2001) found that as early as one month into treatment, changes in markers of bone remodeling, particularly serum carboxy-terminal propeptide of type I collagen (PICP), provided important predictive information of subsequent bone mineral density (BMD) increases in response to FORTEO. BMD is used to both diagnose osteoporosis and monitor treatment effectiveness. Unlike BMD measurements, markers of bone remodeling are able to detect delicate changes in the bone early in the treatment cycle - sometimes within weeks of beginning a treatment.

"These findings are significant because they provide physicians and patients early evidence that treatment with FORTEO is working," said lead investigator Dr. Angelo Licata**, e**ndocrinologist with the Cleveland Clinic**.** "Providing physicians and patients with this information early in their treatment is crucial in that it may help promote compliance, a common roadblock in osteoporosis treatment."

FORTEO, the first and only bone formation agent approved for the treatment of osteoporosis, was granted FDA approval on Nov. 26, 2002. It stimulates new bone formation by increasing the number and activity of bone forming cells called osteoblasts. FORTEO is approved for the treatment of osteoporosis in postmenopausal women who are at high risk for fracture and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men (and postmenopausal women) with a history of osteoporosis-related fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy, based upon physician assessment.

Until FORTEO's approval, the only approved osteoporosis treatments were antiresorptives, which work mainly to slow or stop bone loss by reducing the number and action of bone-removing cells called osteoclasts.

Details

The objective of this sub analysis was to determine if changes in markers of bone turnover could predict increases in BMD at the lumbar spine after 18 months of treatment with FORTEO.

During the study, two markers of bone formation (serum bone-specific alkaline phosphatase [BSAP], PICP) and two markers of bone resorption (urinary free deoxypyridinoline/creatinine ratio [DPD], urinary N-terminal telopeptide/creatinine ratio [NTx]) were assessed, as was lumbar spine BMD.

As was observed in the Fracture Prevention Trial, markers of formation, PICP and BSAP, increased after one month of FORTEO treatment. Levels of PICP for FORTEO 20 mcg and 40 mcg declined after one month and returned to near baseline levels by 12 months. Markers of resorption - NTx and DPD - increased after one month of treatment. All of theses changes were statistically significant from baseline and placebo.

In this analysis, Spearman's correlation coefficient, a formula used to determine the strength of a link between two sets of data, was calculated between bone turnover markers at baseline, one, three and six months and the 18-month lumbar spine BMD

response. Bone turnover status at baseline correlated with subsequent BMD responses for all four markers of turnover. Among all studied biochemical markers, increases in PICP demonstrated the most significant link between increases in lumbar spine BMD and marker levels. These values for PICP at three and six months were significant only for the 40 mcg group compared to placebo. Significant correlations with NTx were seen in those treated with the 40 mcg dose at three and six months. While all other bone turnover markers had weaker associations, overall, the change in PICP at one month was the best predictor of the 18-month lumbar spine BMD response with FORTEO.

Important Safety Information About FORTEO

In two-year studies in rats, teriparatide caused an increase in the incidence of osteosarcoma, a malignant bone tumor, which was dependent on dose and duration of treatment. Although no case of osteosarcoma has been reported in the patients who received FORTEO in clinical trials, it is not known if humans treated with FORTEO are at increased risk for this cancer.

FORTEO should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. The drug should not be prescribed for patients at increased baseline risk for osteosarcoma, including patients with Paget's disease of bone or unexplained elevations of alkaline phosphatase, children or growing adults, or those who have had prior radiation therapy involving the skeleton. Additionally, patients with bone metastases or a history of skeletal malignancies, and those with metabolic bone diseases other than osteoporosis, should not receive FORTEO. Patients with high levels of calcium in their blood should not receive FORTEO due to the possibility of increasing their blood levels of calcium.

In clinical trials, the most frequent treatment-related adverse events reported at the 20-microgram (mcg) dose approved for marketing were mild, similar to placebo and generally did not require discontinuation of therapy. Reported adverse events that appeared to be increased by FORTEO treatment were leg cramps and dizziness (2.6 and 8 percent, respectively), compared with placebo (1.3 percent and 5.4 percent, respectively).

FORTEO is supplied in a disposable pen device that can be used for up to 28 days to give once-daily, self-administered injections. FORTEO is available in a 20-mcg dose and should be taken for a period of up to 24 months. Lilly has implemented a risk management program that includes comprehensive measures regarding the appropriate use of FORTEO in the target patient population. A Medication Guide explaining the details of the drug to the patient also accompanies the product. FORTEO also has a black box warning in its package insert about the osteosarcoma findings in rats during preclinical testing.

About Osteoporosis

More than 50 percent of all women over the age of 75 are estimated to have osteoporosis, and due to their advanced age, have a high risk of fracture. In fact, most American women over the age of 50 will experience one or more osteoporosis-related fractures during their lifetimes, and women with osteoporosis who have two or more previous fractures have up to a nine times greater risk of future fracture compared with women who have not suffered a previous fracture.

About Eli Lilly and Company

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For full prescribing information for FORTEO call 1-800-423-2313.

FORTEO 20 mcg Dosage, Disposable Pen